

## INTRODUCTION

# The Hunt for Immortality

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**Telomere** [TEL-uh-meer, TEE-luh-meer] (noun): the segment of DNA that occurs at the ends of chromosomes.

**Telomerase** [tuh-LO-muh-reys] (noun): an enzyme that causes telomeres to lengthen; facilitates cell division and may account for the immortality of some cells.

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On the morning of October 5, 2009, Carol Greider was at home doing her laundry, thinking about the Spin class she was going to take later on with two female friends. She was tired from long hours at her lab on the campus of the Johns Hopkins School of Medicine and was happy to have a day off. It was a relief to let her mind relax from all the research work and the intense pressure of being one of the country's foremost female scientists.

Then Greider got a very unexpected phone call—the kind of phone call that most professors, most peace activists, and even some world leaders dream about but rarely receive.

After the call, Greider's mind was racing a million miles a second; she wasn't sure what to do. Soon, she figured, she might be getting a few more calls from media organizations and from

friends and colleagues. So the first thing she did was send an e-mail to her fitness-class friends: “I’m sorry I can’t Spin right now. I’ve won the Nobel Prize.”

Greider’s Nobel Prize in medicine was to be shared with her former professor at the University of California–Berkeley, Elizabeth Blackburn, and with Harvard geneticist Jack Szostak. It was awarded to them for the pioneering research they did in the role of telomeres and chromosomes and for the discovery Greider and Blackburn made back in 1984 of telomerase, an enzyme that causes the ends of chromosomes to grow. In reporting on the Nobel Prize, the *New York Times* said that the existence of telomerase has a “deep relevance” for both cancer and aging. In the opinion of the authors of this book, this is, in fact, an understatement. What these remarkable scientists discovered will inevitably lead to a universal cure for all forms of cancer, but even more than this, they have indeed discovered the very secret of immortality.

Contrary to the conventional myth that the only proven ways to extend life expectancy are through severe restrictive practices—such as the calorie-reduction diet—that most can’t and don’t want to follow, there is now a far better, more effective way. Thanks to recent profound breakthroughs in DNA research that go well beyond the initial discoveries that led to the Nobel Prize, it is now possible for you to extend your life expectancy beyond 100 years to 120 or more (perhaps even indefinitely) while leading an active, robust, independent lifestyle, maintaining all the strength and vitality you had when you were much younger. Imagine being a centenarian looking half your age, playing outdoors with your great-grandchildren, dancing with much younger partners, enjoying new hobbies and pursuits, and, yes, still having a great sex life—all without having to worry about life-threatening conditions like cancer, heart disease, diabetes, chronic infections, dementia, poor eyesight, hearing loss, low energy, and the other miserable conditions that plague too many older people. It may sound too good to be true, but it isn’t.

Until now, the concept of immortality was considered forever unachievable. Over time, the cells in our bodies reach a stage at which they can no longer reproduce themselves—a retirement-like state in which they die or no longer divide and thus become inert. This end point is called *senescence*. The effect of senescent cells appears very obviously when they accumulate in quite large numbers in just one tissue (the cartilage in our joints), but even in small numbers they pose a disproportionate, although less obvious, threat to the surrounding healthy tissues because of their steadily deteriorating metabolic state.

Senescent cells secrete abnormally large amounts of certain proteins that are harmful to their neighbors, stimulating excessive growth and degrading normal tissue architecture. These changes appear to promote the progression of age-related diseases, including cancer. (Although cancer sometimes strikes younger people and even children, the overwhelming number of cancer cases occur in the elderly.) Senescent cells in our skin make us look withered. In our immune system, they make us susceptible to the diseases of aging such as heart disease, heart failure, diabetes, and fragility. Even if we are lucky enough to avoid these calamities, eventually so many of our cells will be in a state of senescence that the body as a whole will no longer be able to sustain itself. When this happens, we die of “old age.”

“Death is inevitable!” How many times have you heard this statement?

No matter how well you take care of yourself, what you eat, how great your genes are, or how lucky you are, it is impossible, scientists have thought, for any human being to live past 120. (This is called the Hayflick limit.) Indeed, the oldest man, as far as we have been able to verify without dispute, Christian Mortensen, lived to be 115, and the oldest woman, Jeanne Calment, barely squeaked past the theoretical Hayflick limit by reaching age 122 before passing away in 1997.

At that time, Leonard Hayflick, a professor of microbiology at Stanford University, and other scientists didn’t know exactly

why human cells divided only a limited number of times; perhaps it had to do with free radicals, the accumulation of mutations, a genetic switch that is flipped to the off position after we are too old to reproduce, changes in hormone regulation, the decreased efficiency of the immune system, or even divine providence. No one knew for sure.

Fast-forward to today, and thanks to our Nobel Prize winners and others, we now know exactly why living cells, except cancer cells and germ cells, become senescent, and even more exciting, we know how to increase the number of times cells can divide. In fact, we know how to make normal cells, as opposed to cancer cells, divide and live forever—to indeed become immortal.

This bears repeating. Living cells, including human ones, never have to die, never have to reach senescence. Understanding why isn't that complicated; it has nothing to do with stem cells, the reversal of gene expression, or mitochondria.

As most high school students know (or should know), the nucleus of every single cell in our bodies includes forty-six long twisted strands of DNA on which genes are found. These strands—called *chromosomes*—are organized in pairs, one chromosome in each pair coming from our mother and one coming from our father. Under powerful electronic microscopes, chromosomes look something like very tiny double sausages.

The DNA contained in chromosomes defines everything about us, from our hair color to our gender to the length of our little fingers. Chromosomes are important to all forms of life—indeed, they are found in every living thing, every living cell.

## Solving the End-Replication Problem

When cells divide and multiply, it is very important that the DNA in the chromosomes remains intact; otherwise, genetic defects can occur, some not so serious and others very serious—some even causing cells to become cancerous. For many years, James

Watson, who with his partner, Francis Crick, with contributions from Rosalind Franklin, discovered the double-helix structure of DNA, wondered how DNA is protected when chromosomes divide and multiply. If we lost portions of the information encoded in our DNA every time it replicated, human life would be impossible. Our cells couldn't divide enough times to even allow us to be born. Watson thought about this, because the method a chromosome uses to replicate itself during cell division should, logically, destroy some of the genes at the ends of the DNA. Watson called this the *end-replication problem*.

By the mid-1970s, scientists knew the answer to this puzzle. There was general agreement that both ends of every chromosome contain relatively long strands of "junk" DNA called *telomeres*. The primary function of these telomeres, which consist of up to fifteen thousand repeats (in embryo cells) of the DNA sequence TTAGGG, appeared to be to protect the functional DNA. Thus, when chromosomes divide and multiply, instead of losing the DNA that matters, they lose only some of the telomere's DNA. With every replication of our DNA, part of the telomere sequence is chopped off. This is how nature protects the DNA in a chromosome.

One way to describe telomeres is to compare them to aglets, the plastic caps at the ends of shoelaces. Just as aglets keep shoelaces from falling apart at the end, telomeres keep the ends of DNA from fraying.

Today we can measure the age of cells by the length of the telomeres. Infants have long telomeres, but not quite as long as those found in human embryos. When we are conceived, the embryo has about fifteen thousand base pairs in its telomeres. After many replications, a newborn human is formed and born with approximately ten thousand base pairs in each telomere sequence. Thus, in the uterine development of a human, when cells are dividing furiously to make a newborn baby, five thousand base pairs of telomere length are lost. In a sense, we start to die the minute we are conceived! Adults have shorter telomeres; adults

who are destined to live a long time have longer telomeres than do adults who are destined to live not so long.

There is even a disease of short telomeres: Werner's syndrome, more commonly known as progeria. The unfortunate people who are born with this rare disease age prematurely and have an average life expectancy of only twenty years. Researchers at the University of California–Davis found that male carriers of the gene that causes progeria (Fragile X syndrome), when compared to men their own age, have shorter telomeres than those who aren't carriers.

“Since we adjusted for age, we know that the telomere length is telling us something more than chronological age,” said Dr. Ramin Farzaneh-Far, a cardiologist at the University of California–San Francisco who analyzed the data. “Hopefully it is measuring biological age.”

Researchers at the Albert Einstein College of Medicine of Yeshiva University in New York City made an even bigger breakthrough with a large study of homogeneous Ashkenazi Jews who had previously been genetically studied. Comparing healthy elders who averaged ninety-seven years of age with their children and with the children of Ashkenazi Jews who had died at age eighty or younger, the researchers discovered a link between longevity and the presence of longer telomeres. The children of the older group consistently had longer telomeres than the children of those who had died at age eighty or younger.

Shorter telomeres don't correlate only with age, they also correlate with the stage of one's health. Another study found that among 780 patients with stable heart disease, people with the shortest telomeres in their immune cells had twice the risk of death and heart failure after 4.4 years as did patients with the longest telomeres. Those in the highest-risk group had telomeres half the length of those in the lowest-risk group.

These are just a few of dozens of studies and research projects that correlate telomere length to disease and to death. At this point, telomere shortening has been implicated in almost all aspects

### The FDA Throws Up a Potential Roadblock

In his April 2010 column in *Forbes* magazine, Peter Huber pointed out the insanity of the Food and Drug Administration (FDA) regulations that currently block consideration of potential drugs to treat (that is, prevent or reverse) aging:

For the most part, the FDA still operates under the medical mind-set that prevailed when the federal drug law was amended in 1962. The go/no-go regulatory calls are decided by clinical trials. The key metrics are clinical, like the survival time for a cancer patient. A clear reduction in mortality from a serious disease gets the drug licensed on the double. So far, so good—this panel sounds diligently anti-death. But it's interested only in brinkmanship, at the back end.

The “aging” drugs that the FDA deals with reasonably well are the ones that beat back a single specific disease long after the microscopic seeds of the problem have blossomed into big symptoms. Aging is an incremental, whole-body problem. All cells, tissues and organs age—and in different ways, at different rates, in different people. As defined by their late-stage clinical symptoms, the diseases of old age are legion. At the FDA they will have to be beaten one at a time or not at all. Which means that nobody is ever going to get “antiaging” drugs through the FDA as it currently operates.

of normal aging. High levels of stress hormones, inflammation, insulin, and blood sugar, as well as habits and conditions such as smoking, fatty diets, obesity, and sedentary living, are all linked to shorter telomeres and lower telomerase levels. The conditions and diseases in which short telomeres are found include cancer, atherosclerosis, Alzheimer's disease, osteoarthritis, osteoporosis,

macular degeneration, cirrhosis of the liver, AIDS, and even skin aging.

During the continuum of human life, the trillions of cells that make up a person continue to divide, grow, and replicate. With each cell division, a few base pairs at the tips of the chromosomes (telomeres) are lost, until the critical limit is reached. Then one of two things happens: the cell either enters senescence or commits suicide (apoptosis) and dies. In some people this process happens quickly; in others it can take much longer.

Cells die when telomeres become too short. Leonard Hayflick must have been correct after all—well, actually, no. While scientists were figuring out how telomeres function, they observed two interesting phenomena:

1. Telomere shortening proceeds at an uneven pace—the telomeres of some cells in the same group of cells become much shorter than others.
2. A few telomeres become longer. This was very surprising, because logically, telomere shortening should proceed at a steady pace, and telomeres should never get longer.

Something else was going on here. That something else was the biochemical catalyst, or enzyme, called *telomerase*. The discovery of telomerase was one of those wonderful moments in science history that belies the tediousness of most scientific research. Determined to prove their theory that indeed an enzyme did exist that caused telomere growth, Elizabeth Blackburn, then an ambitious molecular biologist at the University of California–Berkeley, and her second-year graduate student Carol Greider spent most of an entire year conducting failed experiments in which they tried to extract this particular enzyme from innumerable other enzymes in a crude cell extract. They were convinced that the enzyme they pursued was not ephemeral, but their first attempts required a complex process of purification and a long



wait before results could be obtained. These efforts proved to be totally impractical.

Recalling these frustrating months, Greider says, “In the nine months I was doing this, I kept getting negative results. How much longer would I have gone on getting negative results before I would have decided, ‘Well, it probably doesn’t exist?’”

The breakthrough came after Blackburn decided to abandon the laboriously purified plasmid DNA fragments they were using for their experiments and instead try a synthetic and much more concentrated form of DNA called *oligonucleotides*. Within weeks, they obtained the results they had been looking for. On Christmas Day 1984, Greider developed an autoradiogram of their latest batch of DNA. Holding the X-ray image up to the light, she could see a clear pattern of recurring bands that extended like a ladder all the way up the gel. When Blackburn took a look, she noticed right away that the evenly spaced bands were too far apart to represent a random mix of DNA molecules. It was the proof they had been looking for: an enzyme had added telomeric DNA to the ends of the chromosomes.

Blackburn says about this moment, “Thoughts rushed through my mind that this discovery of a new enzymatic activity was as important as the discovery of DNA polymerase. DNA polymerase had garnered a Nobel Prize for its discoverer. I said nothing about this [to Greider], not wanting to raise unrealistic hopes. But we both knew this was it.”

Blackburn and Greider had discovered the little enzyme that could. Many months later, they finally came up with a name for their discovery. They called the enzyme *telomerase*.

Although it would be years before the full significance of telomerase was truly appreciated, we now know that it is present and active in both germ cells and cancer cells, which is one of several reasons these cells never reach senescence. The telomerase gene also exists in all our other cells, because the DNA in every one of our cells is identical—a stem cell, a muscle cell, and

### The Cancer Question

In addition to telomerase providing a way to counter the aging of cells, extensive research into the enzyme has given us many new insights into cancer and its prevention. It is possible to cause cancer cells to die by turning off or inhibiting telomerase, which is giving rise to a whole new class of drugs called *telomerase inhibitors*. Overactivation of telomerase is one of the few constants between almost all types of cancers; it is present in 85% of all cancer cells, whether breast cancer, lung cancer, prostate cancer, or any other cancer. Instead of trying to create dozens of therapies for dozens of different cancers, we could very well be looking at one type of therapy for all types of cancers.

Lest anyone be confused, however, it is important to point out that stimulating the growth of telomeres on normal chromosomes does not cause them to become cancerous. A cancer begins when something else goes wrong in a cell, causing it to lose control over its growth. However, the telomeres continue to shorten in these cells, and very soon these fast-dividing cancer cells will die.

Very occasionally, however, they will find ways to turn on the telomerase gene and relengthen their telomeres. When this happens, a cancer begins to divide not only uncontrollably but also indefinitely. The cancer becomes truly dangerous.

So, turning on the telomerase of normal cells must be highly dangerous, right?

The answer to this question is a resounding *no*. Although telomerase is necessary for cancers to extend their life span, it does not cause cancer. This fact has been repeatedly demonstrated by performing many different types of genetic tests for cancer on telomerase-positive human cells. Scientists have turned on the telomerase of normal cells in attempts to turn these cells into cancer cells, and it just hasn't happened.

Generally speaking, bad things happen when telomeres become short. As cells approach senescence, the short telomeres stimulate chromosome instability, which can cause the mutations that cause cancer. Tumor-suppressor genes can be shut off and cancer-causing genes turned on. The result becomes very dangerous if another mutation causes telomerase to be turned on.

Paradoxically, even though cells require telomerase to become dangerous cancers, turning on telomerase may actually prevent cancer. This is not just because the risk of chromosome rearrangements is reduced, but also because telomerase can extend the life span of our immune cells, improving their ability to seek and destroy cancer cells.

If long telomeres in human beings were correlated with cancer, young people would get cancer more often than the elderly do. However, we usually see cancers occurring in people at the same time they begin to show signs of cellular senescence—that is, at the same time the immune system begins to age and lose its ability to respond to threats. According to the American Cancer Society, 78 percent of all cancers are diagnosed in people fifty-eight years old and older. Extending the life span of our immune cells could help our bodies fight cancer for much longer than they presently do.

a liver cell contain exactly the same genetic information. The crucial difference is that normal cells don't express telomerase, because that gene is repressed in them. The key to immortality is turning the telomerase gene from off to on.

In 1997, scientists inserted active telomerase genes into human skin cells grown in a petri dish. When they observed that the telomerase enzyme was being produced in the cells, as they had hoped it would be, they also observed that the skin cells became immortal. There was no limit to the number of times these cells

could divide. Better yet, when the lengths of these telomerized cells were examined, the scientists were surprised to see that the telomeres didn't just stop shortening, they actually grew longer. The critical question, at the time unanswered, was whether the cells were becoming younger.

A few years later, scientists inserted the telomerase gene into human skin cells that already had very short telomeres. These cells were then grown into skin on the back of mice. As you might expect, the skin from cells that hadn't received the telomerase gene looked like old skin. It was wrinkled, it blistered easily, and it had gene expression patterns indicative of old skin.

The skin grown from cells that had received the telomerase gene, in contrast, looked young. It acted like young skin, and its gene expression patterns were almost identical to the gene expression patterns of young skin. For the first time, scientists had demonstrably reversed aging in human cells.

## A Parts Supply Store for the Human Body

On March 16, 2010, the stock of BioTime, a small biotechnology company in Alameda, California, soared upon the news that the company had induced normal adult human cells not only to reverse their age but also to reverse what is called their *clock of differentiation*. That is, the age of these cells was reversed to the extent that they went all the way back in time to their original state as stem cells. Because stem cells are capable of being regenerated into any type of human cells, this suggests therapies for regrowing heart cells, skin cells, muscle cells, and so on, without having to resort to the highly controversial practice of using embryonic stem cells.

“We are just at the beginning of some really fascinating new possibilities for intervening in age-related disease,” said BioTime’s CEO, Michael West. “What’s exciting about these cells is we now have a way to simply have a master cell bank of the stem cells and

### Why Are We Not Born Old?

Reproductive cells are considered immortal by scientists. This means that they do not age in the normal way that other cells do. Sperm cells divide millions of times, and their telomeres never get short. In sperm cells, the enzyme telomerase adds telomere DNA back to the cells' telomeres and keeps those telomeres as long as they have always been. That's why an eighty-year-old man can still father children. Egg cells, on the other hand, do not divide, and therefore their telomeres do not shorten.

In addition to providing the germ cell with an unending ability to reproduce itself, telomerase also generally keeps the DNA tightly wound (not unraveled), so the cell is not subject to the normal wear and tear that other cells in the body are subjected to.

Thus, reproductive cells do not lose telomere length as we age, and accordingly, babies are born with telomeres the length of babies' and not the length of their parents'. Ultimately, if it were not for telomerase keeping germ cells young, a species would become extinct.

scalably make everything of the human body—like a human parts supply store.”

Just imagine: if your knees wear out, it will someday, in the not-too-distant future, be possible to replace them with real knees rather than artificial ones, and they will be genetically identical to your original knees because they will be able to be grown from your own stem cells!

Biomedical scientist Robert Schwartz from the University of Houston has already demonstrated how to grow human heart cells from adult stem cells that have been harvested from a patient's own skin. These new cells can be implanted and grown into fully

developed beating heart cells, and they will reverse the damage caused by previous heart attacks by replacing the damaged cardiac tissue. So far this work has been done in vitro, but clinical trials using these programmed cells on actual heart patients will begin within a year or two.

Schwartz's vision is similar to Michael West's, only he expresses it differently: "The idea of having your own bag of stem cells that you can carry through life and use for tissue regeneration is at the very cutting edge of science."

New brain cells will someday be used to treat Alzheimer's patients and people with severe brain trauma, or a diabetic could get new insulin-producing cells in the pancreas. Generating a new kidney, lung, or liver will also be possible—even an entire new heart! But we have an even loftier goal in creating the Immortality Edge program. We want to give you the possibility of being forever young so that your body doesn't wear out or become disease-ridden. If you can keep your telomeres long enough, and even grow them to be longer, you will never have to face the deterioration of getting old. You'll instead remain forever young.

## How Will the Earth Hold Us All?

One of the first questions that invariably comes up during discussions of life extension or anti-aging strategies is "What will we do with all the people?"

It stands to reason that life extension and immortality would increase the world population; after all, we've seen it happen before. In just over a century, the average life expectancy of a person living in the United States has increased from 47.3 years in 1900 to 78 years in 2008. Technologies—including vaccines, antibiotics, chemotherapy, and antioxidants—as well as social advances

such as sanitation, environmentalism, and an antismoking crusade have all contributed to this. Most recently, we've made attempts to push our life expectancy even further with technologies such as hormone replacement, caloric restriction.

These technologies have indeed increased the size of our population. But something interesting also happened: the population growth rate began to slow down. Birthrates fell rapidly, and in less than four decades, the average number of children in a family in the United States was more than cut in half, from 6 to 2.9. Today, most leading population researchers think that the world is headed quickly toward a stable population. Evidence is mounting that humans will simply not reach populations larger than our ability to sustain them; economics precludes us from doing that. As resources become scarce, prices rise, and as prices rise, family sizes shrink.

Is it a bad thing that our medical advances have nearly doubled our life expectancy? Most would say it's a decidedly good thing. So it's probably a safe bet that if we can drastically increase that figure again, future generations will also look back on it as beneficial.

Let's be realistic, too, about how many people will take the time to understand the telomere biology in this book and adopt the strategies we recommend for slowing down or even reversing telomere shortening. Unless *The Immortality Edge* outsells the Bible, we don't have much to worry about.

If tomorrow morning the scientists at Sierra Sciences, a company based in Reno, Nevada, that searches for telomerase inducers, announce that they have found the perfect compound for switching on telomerase, how long will it take to get this compound developed into a drug, tested, approved by the FDA, and put into the marketplace in large enough quantities to make much of a statistical difference in world population?

How many people even want to live an indefinite life span? We think it is sad that most people accept death as inevitable, and it

will be a very long time before the majority realizes that this is no longer the only option.

## Death Is Not Inevitable

Each of us carries within the self a unique and complex universe of knowledge, skills, wisdom, life experiences, and human relationships. Almost all of this rich treasury of information is forever lost when someone dies. As famed neuroscientist Anders Sandberg likes to point out, “Every time a human being dies, a library burns. It is a horrible tragedy that all our life experiences get lost, both the good and the bad.” It is worth stating again and again: death is not inevitable.

“In the same way we have one-hundred-year-old cars that are working just as well as they did when they rolled off the production line,” says Aubrey de Grey, the Oxford biogerontologist who is often considered the leader of the entire anti-aging movement, “once we are able to implement comprehensive repair [and] maintenance technologies, we’ll be able to do the same for the human body. The first human being to live to one thousand is already among us.”

If you believe that you have no purpose in life and nothing much to contribute to other people, then this book is not for you. However, if you love living and still have many things you would like to accomplish, then living as long as possible will let you achieve more and become a more valuable person. You’ll have time, metaphorically speaking, to build the city of Rome all by yourself!

What could be better than this? What do you have to do to live as long as you want? As you’ll soon discover by reading *The Immortality Edge*, there are many ways to keep your telomeres long and healthy. You can start today by eating telomere-friendly foods, exercising the right way, meditating, taking supplements that have been linked to longer telomeres, and making some



other lifestyle changes we recommend. There is even a pill you can take that has been proven to lengthen telomeres. It's all right here.

If you let us help you stay healthy, vital, and young for only an extra ten to twenty years, we have no doubt whatsoever that new medical therapies (for example, regenerative medicine) and new supplements will be available that will not just slow telomere shortening but will reverse it. It will actually be possible for you to become biologically younger and to live indefinitely.

For the winter holiday season of 2084, we plan to organize a celebration on the Island of Fiji to celebrate the one-hundredth anniversary of Elizabeth Blackburn and Carol Greider's discovery of telomerase; incidentally, this will also be the seventy-fourth anniversary of the publication of this book. By reading *The Immortality Edge*, you're automatically invited to join us and be part of the first significant group of human beings to blast through the Hayflick limit.

We hope to see you there.

### The Quick Telomere Age Test

This test will give you a rough idea of what your telomere age is. For a more accurate result, take the complete test in chapter 5.

Start with your chronological age and add or subtract from it based on the answers to the following questions:

1. Do you exercise for at least forty-five minutes three or more times a week? If yes, subtract five years.
2. Do you smoke cigarettes? Add ten years.
3. Do you currently drink three or more drinks of alcohol on a daily basis? Add seven years.
4. Do you sleep between seven and nine hours most nights? Subtract five years.

5. If you are male and your waist is less than thirty-six inches, subtract five years. If you are female and your waist is less than thirty-two inches, likewise, subtract five years.
6. Do you take fish oil? If you take 3,000 milligrams a day or more, subtract five years.
7. Generally speaking, are you happy? Subtract seven years.
8. Do you eat fried foods more than twice a week? Add three years.